REMARKS

Claims 4-6 are pending in the instant application. New claims 7-11 have been added with this action. Support for new claims 7-11 can be found at page 6, lines 13-26, and at page 7, lines 1-7, as well as throughout the application as filed. Accordingly, new claims 7-11 add no new matter. Applicants acknowledge removal of finality of the previous Office Action pursuant to 37 CFR 1.114.

Applicants respectfully request that the following Response to the Final Rejection of record dated August 26, 2003 be considered prior to the substantive examination of the accompanying Request for Continued Examination (RCE) filing under 37 CFR §1.114. This Response After Final, accompanying the filing of an RCE, has been made timely by the filing of a Petition for a Three Month Extension of time and payment of fee. This Response After Final presents a bona fide attempt to advance the application, as required under 37 CFR §1.111 for RCE filings if a reply to an Office action is outstanding.

I. *The claims are valid under 35 U.S.C. §103*

Claims 4-6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Metelev *et al.* (U.S. Patent No. 6,143,881) in view of Ghosh *et al.* ((1993) Anti-Cancer Drug Design 8(1): 15-32). In particular, the Office Action states that "one of ordinary skill in the art would have been motivated to combine the phosphorothioate-phosphodiester oligonucleotide co-polymer design taught by Ghosh *et al.* into the hybrid oligonucleotide taught by Metelev *et al.* to obtain the benefits of antisense design taught by each Ghosh *et al.* and Metelev *et al.*" Applicants respectfully traverse this ground of rejection for the reasons that follow.

Applicants respectfully note, again, that no specific motivation to combine the cited references has been shown in either Metlev *et al.* or the Ghosh *et al.* references. Rather, the Office Action broadly asserts that "the properties of the Ghosh *et al.* and the Metelev *et al.* dovetail and, therefore, would be obvious to combine for the skilled artisan." Applicants respectfully assert that, lacking the demonstration of a motivation to combine the cited

references, the benefit of hindsight is being used to justify rejection of Applicants' claimed hybrid oligonucleotides.

Furthermore, it is well established law that a proposed modification or combination of prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991) (where the idea of using a monkey gene to probe for a homologous human gene may have been "obvious to try," but was not obvious under 35 U.S.C. §103 because many pitfalls existed that would have precluded a "reasonable expectation of success."). Therefore, even accepting the logic of the rejection that the instant invention was "obvious to try" as a combination of elements taught by different references, nevertheless a reasonable expectation of success was lacking and so the claim is not obvious under 35 U.S.C. §103.

Applicants further note that, not only was there neither motivation to combine the teachings of Ghosh *et al.* with the teachings of Metelev *et al.* to arrived at the claimed invention, nor a reasonable expectation of success from making such a combination, but there was also knowledge in this field at the time of the invention that would have taught researchers *away* from making the claimed combination. In particular, Applicants note that the state of the art at the time of the invention recognized a problem that arose when administering phosphorothioate oligonucleotides to non-human primates, namely the activation of the immune complement system (see Henry *et al.* (1997) J. Pharmacol. Exp. Ther. 281:810-816 (see Suppl. IDS included with this response)). The activation of immune complement in primate subjects (including humans) would result in toxicity, an obviously undesirable property for a therapeutic olignoucleotide.

Therefore the state of the art at the time of the invention taught away from combining the phosphorothioate-containing oligonculeotides of Ghosh *et al.* with the 2'-O-methyl ribonucleotides of Metelev *et al.* because: (1) the Metelev *et al.* oligonucleotides carrying 2'-substitutions had already solved the problems of improving duplex formation with RNA, nuclease stability *in vivo* and RNase H activation (therefore, there was no reason to add the

teachings of Ghosh *et al.*); and (2) the state of the art recognized that phosphorothioate oligonucleotides caused undesirable toxic immune responses (therefore, there was reason not to add the teachings of Ghosh *et al.*).

The Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents strong evidence of unobviousness. *See In re Hedges,* F.2d 1038, 1041 (Fed. Cir. 1986). Indeed, Applicants phosphorothioate-containing POPS-block oligonucleotides have proven to have unexpectedly little adverse immune effect, while still providing the advantages of stability and hybridization efficiency seen with phosphorothioate oligonucleotides. Therefore, because the prior art taught away from making the hybrid phosphorothioate-containing oligonucleotides of the invention, and, further, because the claimed invention had unexpectedly desirable properties in this regard, the claims are not obvious under 35 U.S.C. §103.

Finally, as still further evidence for the nonobviousness of the claimed invention, Applicants provide herewith the results of experimental analyses showing that the hybrid oligonucleotides of the invention have unexpectedly desirable properties of nuclease stability, while uniquely avoiding deleterious immune-mediated toxicity (see Exhibits B-1 through B-6).

Table 1, shown below, summarizes the results of these studies. Briefly, the results show that an unmodified, all-phosphodiester-linked oligonucleotide (GEM 231), while able to avoid undesirable activation of complement, is not at all stable against nucleases found in bovine serum (compare Exhibit A-1 to A-2 (0% stable)). In contrast, GEM 231 oligonucleotide containing both 2'-O-Me-modified nucleosides and an all-phosphorothioate backbone is very resistant to nuclease degradation (compare Exhibit A-3 to A-4 (95% stable)).

However this all-phosphorothioate oligonucleotide is immunogenic and would cause deleterious activation of complement in a treated subject. Surprisingly, the introduction of alternating phosphodiester/ phosphorothioate linkages into GEM 231 allows the structure to retain most of its nuclease stability (compare Exhibit A-5 to A-6 (57% stable)), while avoiding the deleterious immune effects seen with all-phosphorothioate oligonucleotides, as well as the

decreased duplex stability seen with all-phosphorothioate oligodeoxyribonucleotides. Other POPS block-containing oligonucleotides had similar properties (data not shown).

TABLE 1

EXHIBIT	OLIGONUCLEOTIDE	STRUCTURE[1]	RELATIVE STABILITY[2]
A-1 & A-2	GEM 231-PO	5'-GoCoGoUoGoCoCoToCoCoToCoAoCoUoGoGoC-3'	0%
A-3 & A-4	GEM 231 -2'-O-Me-all-PS	5'-GsCsGsUsGsCsCsTsCsCsTsCsAsCsUsGsGsC-3'	95%
A-5 & A-6	GEM 231 -2'-O-Me-POPS	5'-GsCoGsUoGsCoCsToCsCoTsCoAsCoUsGoGsC-3'	57%

1. Internucleoside linkages are indicated as "s" for phosphorothioate linkages and "o" for phosphorothioate linkages; 2'-O-methylribonucleoside residues are underlined.

2. Relative stability is the percent of intact oligonucleotide remaining following incubation with 10% fetal bovine serum at 37° C for 24 hours.

Therefore, in light of the lack of motivation to combine the teachings of Metlev *et al.* and Ghosh *et al.*, the lack of a reasonable expectation of success when making such a combination at the time of the invention, the perception within the field at the time of the invention that such a combination would result in adverse immune effects, and, still further, the presence of unexpectedly advantageous properties of the claimed hybrid oligonucleotides, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

This Response is being filed with an RCE and a petition for a three-month extension of time, up to and including February 26, 2004. Applicants believe no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,

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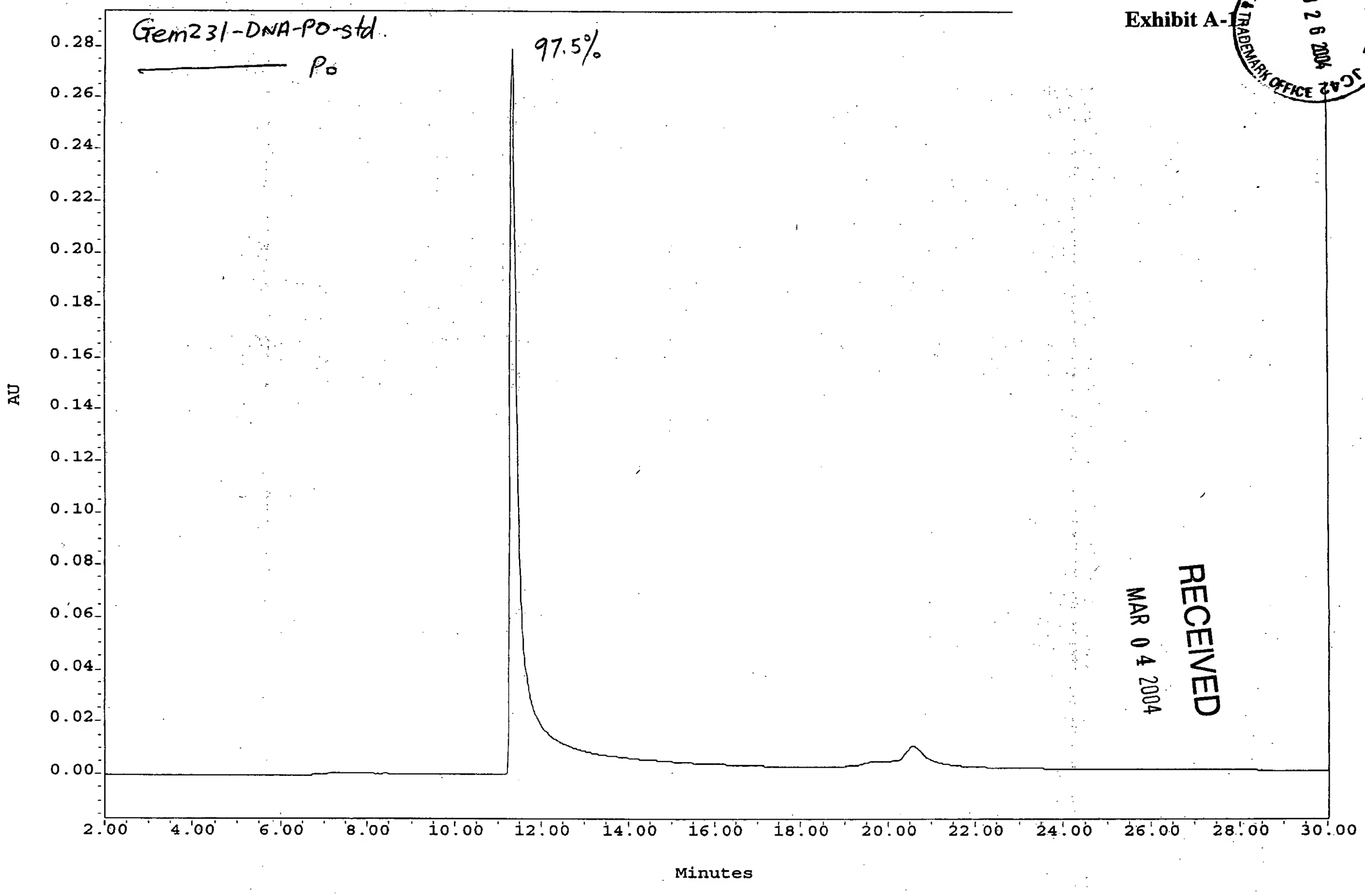
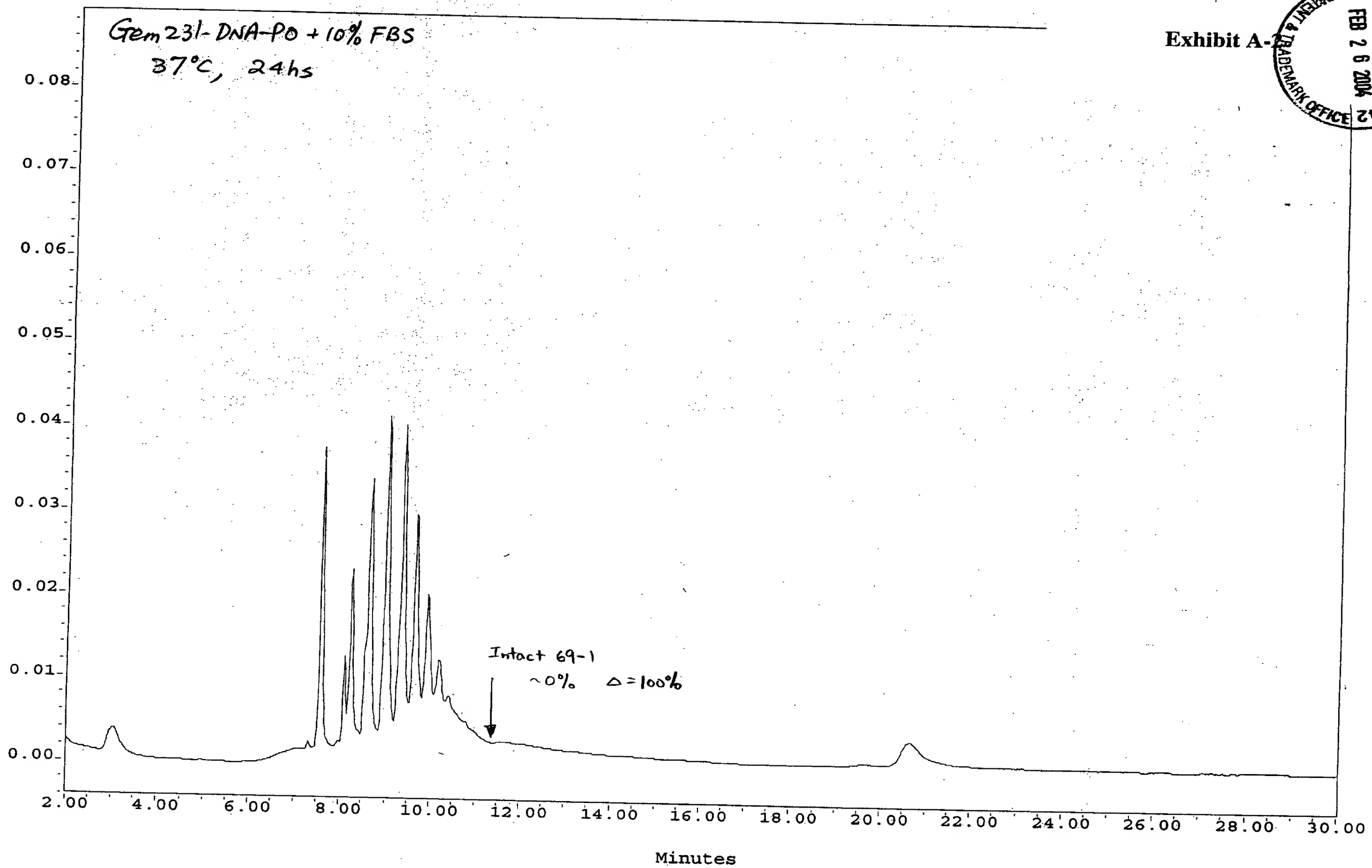
Exhibit A-1



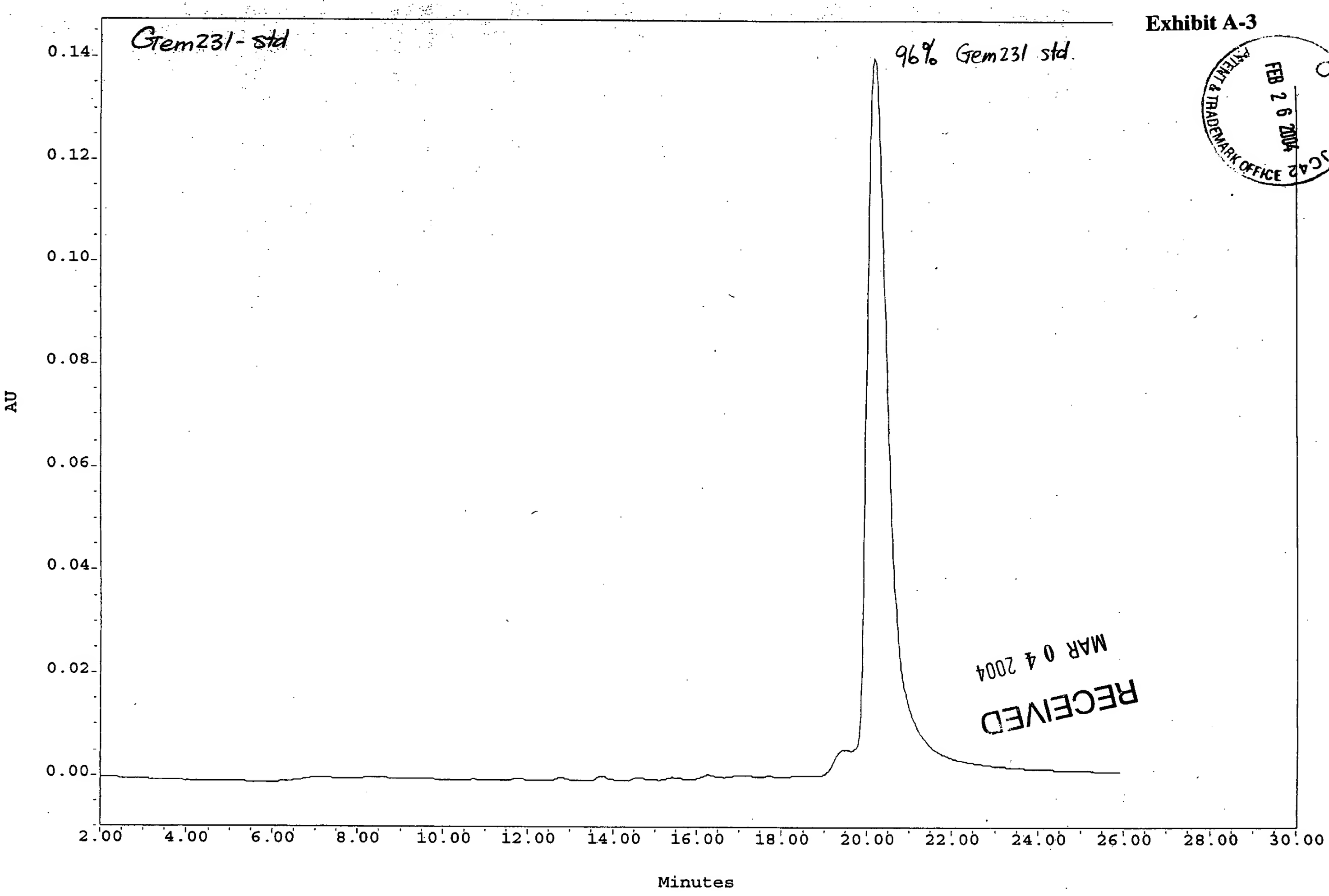
SampleName: 69-1-std Vial: 1 Inj: 1 Ch: 265 Type: Unknown

Exhibit A-2



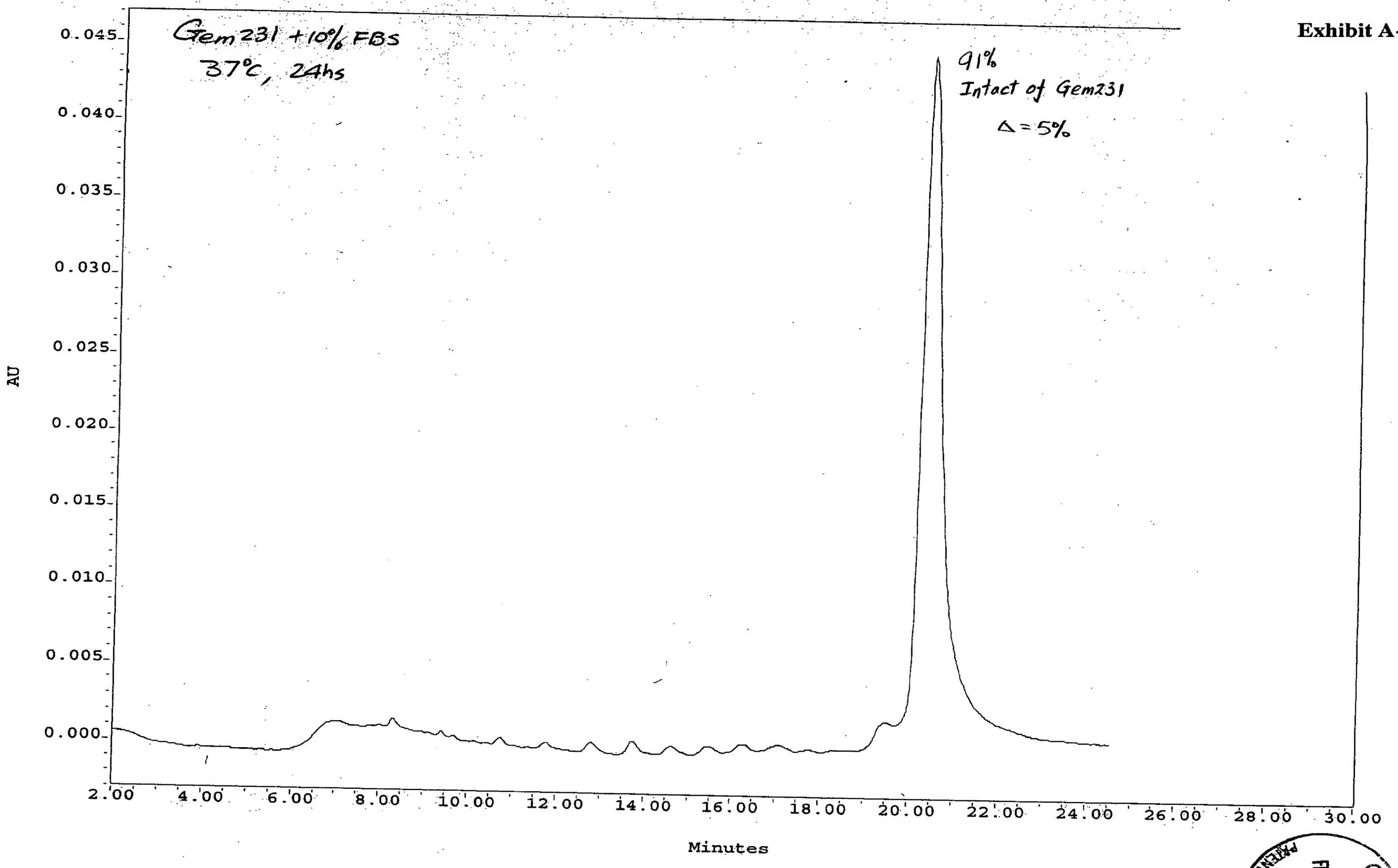
SampleName: 69-1-dig1 Vial: 2 Inj: 1 Ch: 265 Type: Unknown

Exhibit A-3

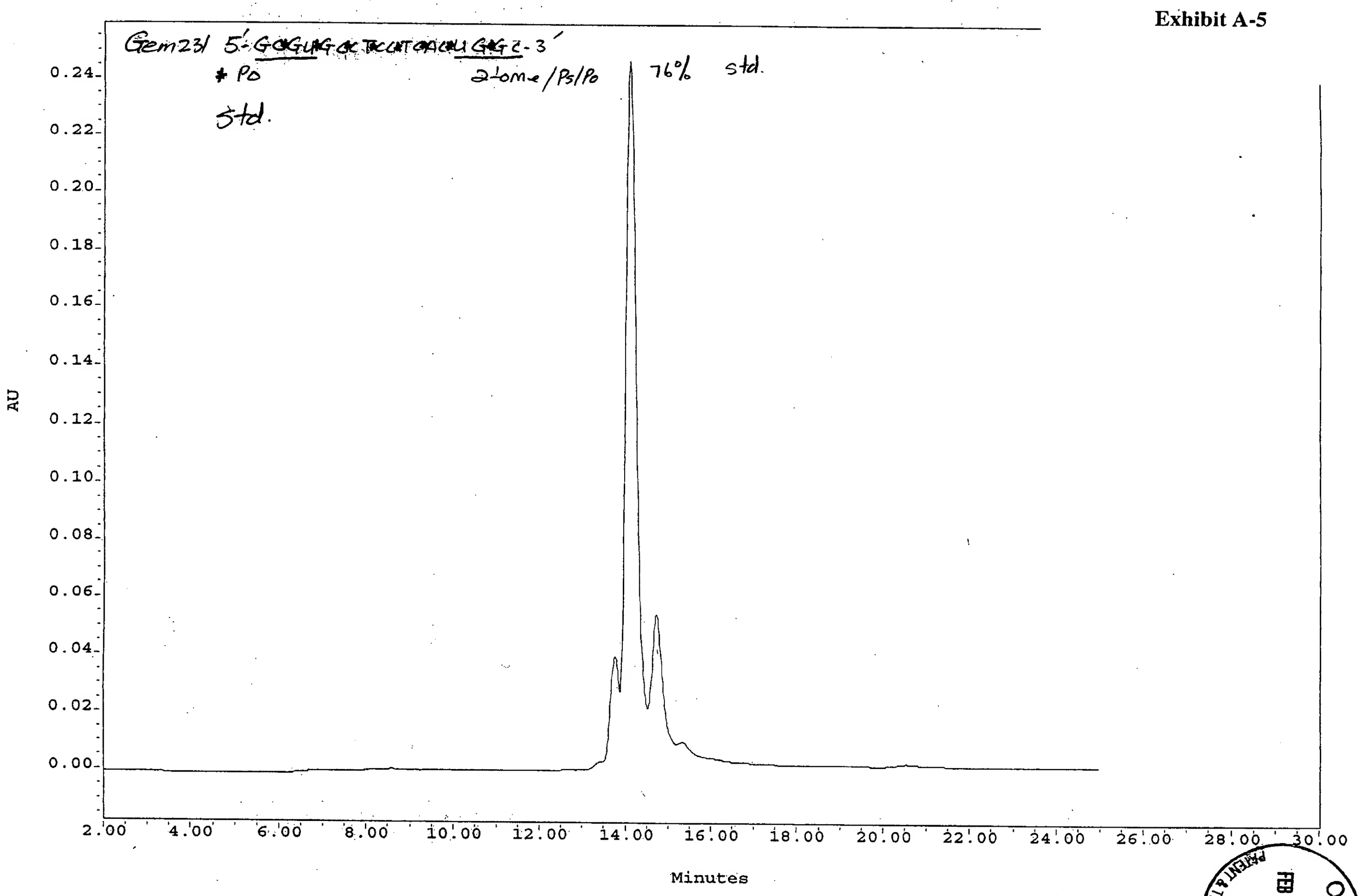


SampleName: 231-std Vial: 5 Inj: 1 Ch: 265 Type: Unknown

Exhibit A-4



SampleName: 231-dig Vial: 6 Inj: 1 Ch: 265 Type: Unknown



SampleName: 69-3-std Vial: 10 Inj: 1 Ch: 265 Type: Unknown

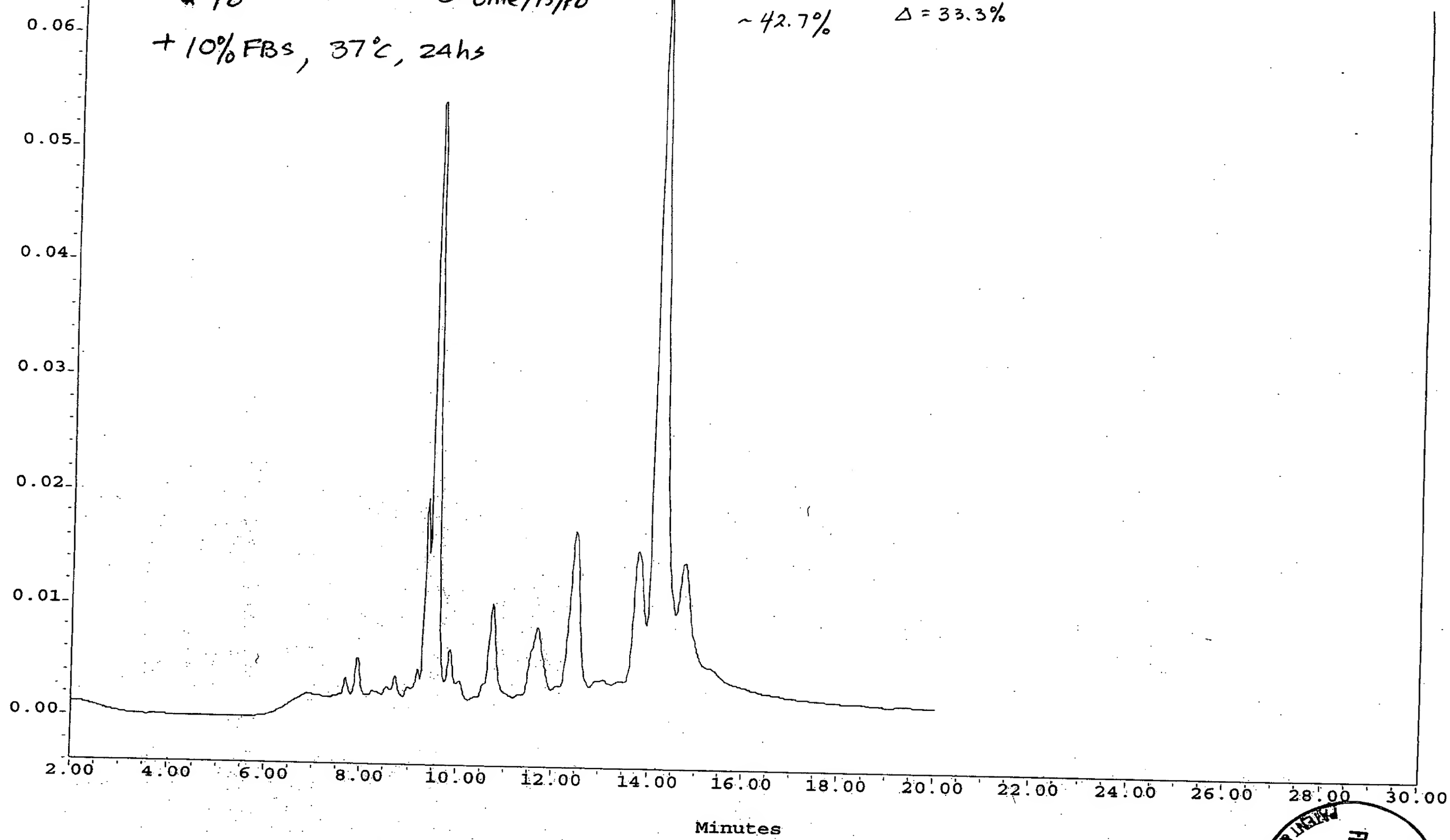
Gem231 5'-GC*GU*G*C*T*C*T*C*A*C*U*G*G*C-3'

* Po 2'-ome/Ps/Po

+10% FBS, 37°C, 24hs

Intact of 69-3

~42.7% Δ = 33.3%



SampleName: 69-3-dig Vial: 9 Inj: 1 Ch: 265 Type: Unknown